REMARKS

A. Objections to the Drawings

Corrected formal drawings will be submitted upon receipt of the Notice of Allowability.

B. Abstract

The examiner noted that the present application was filed without an abstract, but that the examiner would place the published abstract from PCT/US96/18984 into the application as page number 70. Applicants concur with this action.

C. Sequence Non-compliance

Enclosed herewith are a paper copy and a computer readable form (CRF) copy of the SEQUENCE LISTING for the above-identified application. Both are filed to conform the instant application to the requirements of 37 C.F.R. §§ 1.821 - 1.825. The contents of the paper version of the SEQUENCE LISTING and the computer readable form are the same and do not include new matter.

D. Status of Claims

Reconsideration of this application as amended is requested. Claims 22-23, 25 and 29 are amended and claim 34 is cancelled herein. Claims 22-26, 29 and 32-33 are pending. No new subject matter has been added.

The amendments to the claims are fully supported by the specification as originally filed. The amendments are made to clarify the claims, and are not intended to limit the scope of equivalents to which any claim element may be entitled.

Claims 22 and 29 have been amended to clarify that lipid A of the mutant endotoxin is the same as lipid A of the wild type endotoxin except for the fact that the lipid A of the mutant endotoxin lacks at least one secondary acyl chain on lipid A as compared to the wild type endotoxin. Support for this amendment can be found throughout the specification. For example, Figure 1 depicts lipid A from a wild type endotoxin (hexaacyl), and Figures 2A and 2B depict lipid A from mutant endotoxins of the invention (pentaacyl and tetraacyl, respectively). *See also*

Brief Description of the Figures on page 5 of the specification. The only change between Figure 1 and Figures 2A/2B is a decrease in the number of secondary acyl chains in the lipid A. There is no other change in the lipid A (such as length of the remaining chains). Further, page 4, lines 18-25 of the specification states that the lipid A produced by the mutant lacks one or both of the fatty acids, which renders the endotoxin substantially reduced in toxicity while still retaining antigenicity as compared to wild type. Page 11, lines 16-23 states that the lipid A of the mutants specifically lack one or more secondary acyl chain fatty acids that are ester-bound to the hydroxyl groups of two of the four molecules of β-OH. Moreover, on page 18, lines 5-8 of the specification states that the lipid A structure of the mutant endotoxin has one or two fewer acyl chains than the wild type.

Claim 22 has also been amended to recite that the mutant endotoxin is purified from the mutant gram-negative bacterial pathogen. Support for this amendment is found in previously pending claim 34.

Claims 23 and 25 have been amended as suggested by the Examiner at page 10 of the Office Action.

E. Non-Statutory Double Patenting Rejection

The Examiner rejected claims 22-23, 25, 29, 32 and 34 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-20 and 22 of U.S. patent application Serial No. 08/565,943. Applicants will consider filing a terminal disclaimer upon notification of otherwise allowable subject matter. A terminal disclaimer may not be appropriate once the scope of allowable claims is determined in the present application, and dependent upon which application is allowed first.

F. Rejection of Claims 22-26, 29 and 32-34 under 35 U.S.C. §112, First Paragraph (Enablement)

The Examiner rejected claims 22-26, 29 and 32-34 under 35 U.S.C. § 112, first paragraph, indicating that these claims are non-enabled with regard to the deposit of Gram negative bacterial pathogens. The examiner states that one of the deposited *htrB* mutant strains,

B29, produces an endotoxin that shows two clearly discernible differences in the PEA and hexose contents as described in the paragraph bridging pages 16 and 17 of the specification. The claims have been amended to clarify that lipid A of the mutant endotoxin is the same as lipid A of the wild type endotoxin except that the lipid A of the mutant endotoxin lacks at least one secondary acyl chain as compared to the lipid A of the wild type endotoxin. The complete endotoxin molecule (*i.e.*, including the other moieties of the molecule beyond the lipid A portion) may or may not have additional changes.

In addition, the Examiner states that the scope of the claims broadly encompasses *htrB* mutants of any gram negative bacterial pathogens, including any species of *Pseudomonas, Campylobacter, Moraxella, Neisseria* and *Haemophilus,* all allegedly capable of producing a mutant endotoxin of substantially reduced toxicity compared to the endotoxin of a wild-type bacterial pathogen of the same species as the mutant pathogen. The Examiner further states that it does not appear that the recited mutant bacteria are publicly available, or can be reproducibly isolated from nature without undue experimentation.

Applicants assert that the pending claims fully meet the enablement requirement. The purpose of the enablement provision is to assure that the inventor provides sufficient information about the claimed invention so that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and the knowledge in the art. *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 U.S.P.Q. 2d 1001, 18 U.S.P.Q.2d 1896 (Fed. Cir. 1991). It is well-settled that there is no requirement for working examples to fulfill the requirements of 35 U.S.C. §112, first paragraph, if the invention is otherwise disclosed so that one of ordinary skill in the art can practice the invention without undue experimentation. *In re Robins*, 429 F.2d 452, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970); *In re Borokowski et al.*, 422 F.2d 904, 164 U.S.P.Q. 642, 645 (C.C.P.A. 1970). Applicants need not demonstrate the efficacy of all species of gram negative pathogens in order to be entitled to a generic claim of reasonable scope.

Applicants submit that practitioners in the art related to the present application would be well-equipped to make and screen the mutant gram negative bacterial pathogens of the present invention. The lipid A moiety of the endotoxin is highly conserved among bacteria of the family

Enterobacteriaceae and closely related gram-negative bacteria. Specification at page 11, lines 34-35. Thus, one of ordinary skill in the art would expect that any gram-negative bacterial pathogen would be capable of producing a mutant endotoxin of substantially reduced toxicity as compared to the endotoxin of a wild type bacterial pathogen of the same species. Further, Applicants clearly teach that the mutant endotoxin is a result of the bacterium containing a mutant *htrB* gene that is unable to encode a functional HtrB enzyme. The specification of the present application presents a detailed description of how to make the claimed invention using standard mutagenesis techniques (pages 12-15 and 38-53 of the specification), and teaches that one of ordinary skill in the art can use standard methods to screen the resulting products (*e.g.*, mass spectrometry, pages 16-18 of the specification). Further, Applicants provide illustrative examples for *Haemophilus* in Examples 1-3 of the specification. Applicants provide evidence of additional experiments involving *Neisseria* in the Declaration of Drs. Gibson and Apicella under 37 C.F.R. § 1.132 that was filed in U.S. Patent Application Serial No. 08/565,943 (submitted on June 30, 2000, hereinafter "Declaration under 37 C.F.R. § 1.132") (a copy of which is attached hereto). The present application is a national stage filing under 35 U.S.C. § 371 of international patent application PCT/US96/18984, filed November 27, 1996, which in turn is an international filing of U.S. Patent Application Serial No. 08/565,943. In this Declaration, they provide evidence that the outcome for a knockout *htrB* gene in *N. gonorrhoeae* is similar to the outcome for an *htrB* knockout gene in *H. influenzae*, which produced a truncated pentaacyl and tetraacyl lipid A species. Declaration under 37 C.F.R. § 1.132 at ¶ 5.

Thus, Applicants have provided the necessary methods, including examples on how to test for *htrB* mutant gram negative bacterial pathogen endotoxins, wherein the lipid A of the mutant endotoxin is the same as lipid A of the wild type endotoxin except for lacking at least one secondary acyl chain on lipid A. Because mutagenesis methods and screening methods are well-known by those of skill in the art, undue experimentation is not required to practice the invention recited in the pending claims. The inventor has provided sufficient information about the claimed invention so that a person of skill in the field of the invention can make and use it without undue experimentation, relying on the patent specification and knowledge in the art.

Therefore, the claims as currently amended are fully supported by the specification, and comply with the enablement requirement of 35 U.S.C. §112, first paragraph. Thus, withdrawal of the enablement rejection under 35 U.S.C. § 112, first paragraph is respectfully requested.

G. Rejection of Claims 22-26, 29 and 32-34 under 35 U.S.C. §112, First Paragraph (New Matter)

The Examiner rejected claims 22-26, 29 and 32-34 as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors at the time the application was filed, had possession of the invention. The Examiner states that the recitation "wherein the mutant endotoxin is the same as wild type endotoxin except for lacking at least one acyl chain on lipid A" is not supported by the specification as originally filed.

The claims have been amended to clarify that lipid A of the mutant endotoxin is the same as lipid A of the wild type endotoxin except for that it lacks at least one secondary acyl chain as compared to the wild type endotoxin's lipid A. The complete endotoxin molecule (*i.e.*, including the other moieties of the molecule beyond the lipid A portion) may or may not have additional changes. Figure 1 depicts lipid A from a wild type endotoxin (hexaacyl), and Figures 2A and 2B depict lipid A from mutant endotoxins of the invention (pentaacyl and tetraacyl, respectively). *See also*, Brief Description of the Figures on page 5 of the specification. The only change in the endotoxin's lipid A between Figure 1 and Figures 2A/2B is a decrease in the number of secondary acyl chains. There is no other change in the lipid A (such as length of the remaining chains). Further, page 4, lines 18-25 of the specification states that the lipid A produced by the mutant lacks one or both of the fatty acids, thereby rendering the endotoxin substantially reduced in toxicity, and yet retaining antigenicity as compared to wild type. Page 11, lines 16-23 states that the lipid A of the mutants specifically lack one or more secondary acyl chain fatty acids that are ester-bound to the hydroxyl groups of two of the four molecules of β-OH. Moreover, on page 18, lines 4-8 of the specification states that the lipid A structure of the mutant endotoxin has one or two fewer acyl chains than the wild type.

The examiner also indicates that there is no descriptive support within the specification for an "*htrB* gene encoding a wild type endotoxin." This phrase has been cancelled, thereby rendering this rejection moot.

Therefore, the claims as currently amended are fully supported by the specification, and do not introduce new matter.

H. Rejection of Claims 22-26, 29 and 32-34 under 35 U.S.C. §112, First Paragraph (Written Description)

The Examiner has rejected the pending claims as containing subject matter that was not described in the specification in such as way as to reasonably convey to one skilled in the relevant art that the inventors an the time the application was filed had possession of the claimed intention. In particular, the Examiner states that there is no written description teaching a method of making an endotoxin or a method of making an *htrB* mutant gram negative bacterial pathogen wherein the endotoxin is the same as wild type endotoxin except for lacking at least one secondary acyl chain on lipid A.

The claims have been amended to clarify that lipid A of the mutant endotoxin is the same as lipid A of the wild type endotoxin except for that it lacks at least one secondary acyl chain. The complete endotoxin molecule (*i.e.*, including the other moieties of the molecule beyond the lipid A portion) may or may not have additional changes. Adequate written description of the invention as presently claimed is found throughout the specification.

Therefore, the claims as currently amended are fully supported by the specification, and thus comply with the adequate description requirement of 35 U.S.C. §112, first paragraph.

I. Rejection of Claims 22-26, 29 and 32-34 under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 22-26, 29 and 32-34 under 35 U.S.C. § 112, second paragraph, as being indefinite.

(a) The Examiner stated that claim 29 was vague and confusing in the recitation of "an *htrB* mutant of a gram-negative bacterial pathogen, endotoxin isolated from the *htrB* mutant of the gram-negative bacterial pathogen, or endotoxin purified from the *htrB* mutant of the

gram-negative bacterial pathogen" for immunizing an individual for the production of endotoxin-specific antisera. According to the Examiner, it is not clear whether or not the antisera produced is specific for wild-type endotoxin or *htrB* endotoxin (page 9 of the Office Action). Claim 29 has been amended to recite "*htrB* mutant endotoxin," thereby overcoming the Examiner's rejection of claim 29.

(b) The Examiner stated that 22 is vague, indefinite and confusing because it is unclear how mutating a *htrB* gene in a bacterium would "provide" a mutant endotoxin. The claim has been amended to clarify that the mutant endotoxin is produced by mutating an *htrB* gene in gram-negative bacterial pathogen and purifying the mutant endotoxin from the mutant gram-negative bacterial pathogen, thus overcoming this rejection of claim 22.

(c) The Examiner has indicated that claim 29 is confusing and that the scope is indeterminate, as the specificity of the antibody collected in step (b) of the claim is unclear. Claim 29 has been amended to clarify that the antibody collected is specific for mutant HtrB, thus overcoming this rejection of claim 29.

(d) The Examiner has indicated that claims 23 and 25 do not recite proper antecedent basis. The claims have been amended as suggested by the Examiner.

(e) Claims 24, 26 and 32-34, which depend directly or indirectly from claim 22 or claim 29, were also rejected as being indefinite because of the indefiniteness identified above in the base claims. Applicants have now amended the claims to address the indefiniteness issues raised by the Examiner, and therefore has overcome this rejection.

The claims as currently amended are fully supported by the specification, and thus comply with the requirements of 35 U.S.C. §112, second paragraph. Therefore, these rejections should be withdrawn.

CONCLUSION

Applicants believe that all claims are in condition for allowance. Reconsideration of the rejections of the claims and allowance of all the claims is respectfully requested. The Examiner is invited to contact the Applicants' attorney, Ann S. Viksnins (612-373-6961), or the underesigned if prosecution of the present application can be assisted thereby.

Respectfully submitted,

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Date 3 September 2003

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Commissioner for Patents, P. O. Box 1450 Alexandria, VA 22313-1450, on this 3rd day of September 2003.

Candis B. Buending
Name

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Signature